REMARKS

Claims 36, 39, 42, 45 and 48 are pending this application. The Examiner has rejected these claims under 35 U.S.C. § 112, first paragraph. The Examiner maintains that undue experimentation is required to practice the claimed invention given that no examples are provided of catalytic antibodies, the broad category of haptens covered in the claims and the unpredictability of the art. The Examiner states that the reference, Gao et al., while showing a trigonal boronic hapten will produce a catalytic antibody, does not disclose the same hapten as that of the instant claims.

Applicants respectfully submit that the specification provides sufficient disclosure to enable a person of ordinary skill in the art to practice the claimed invention. The disclosed trigonal boron-containing hapten is enabled for eliciting catalytic antibodies without undue experimentation. The disclosure of methods of synthesis to prepare the disclosed haptens is sufficiently detailed to enable one of ordinary skill in the art to synthesize the claimed haptens.

Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed or whether an example is working or prophetic in nature (MPEP Section 2164.02). The fact that experimentation may be necessary and/or complex does not mean that it is undue if the art typically engages in such experimentation. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) (MPEP 2164.01).

Applicants submit that the claimed haptens and the hapten of Gao et al. (Gao) are sufficiently similar that that one of ordinary skill in the art can generate catalytic antibodies with the disclosed haptens using similar protocols. The crucial similarity is the use of a trigonal boronate linkage as an amide analog. This type of chemical bond configuration mimics the bond to be cleaved or formed and makes it an effective transition state analog.

The functional difference between the Gao hapten and the claimed hapten is revealed by the selectivity of the reactions they catalyze. The Gao haptens are designed to generate catalytic antibodies that cleave or form primary amides at the peptide termini whereas the claimed haptens are designed to elicit antibodies that cleave or form internal peptide bonds. Given the disclosure in the specification and the similarity of these haptens one of ordinary skill in the art can generate catalytic antibodies that hydrolyze or form internal peptide bonds without undue experimentation.

The examiner's statement that catalytic antibody art is unpredictable and that the Gao reference is indicative of such unpredictability is hereby traversed. In discussing catalytic antibody technology, Gao teaches "while this approach has proven largely successful for over 50 chemical reactions, there are some transformations which have proved resistant to this methodology" (page 2211). Gao further elaborates when describing his methodology that "the key selection step is linked to antibody recognition of the trigonal α-amino boronic hapten **3a**..." (page 2214).

The claimed invention utilizes the boronate in the similar trigonal coordination configuration as in Gao. Even assuming, *arguendo*, that some chemical transformations are resistant to catalytic antibody methodology, Gao's statement indicates that that is not the case for amide bond hydrolysis when a trigonal boronic hapten is used.

Applicants also maintain that to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, it is not necessary that every hapten result in the successful generation of catalytic antibodies in every case. The specification discloses how to make the haptens, how to use the haptens to generate catalytic antibodies and how to test the catalytic antibodies for the desired activity. The disclosures in the specification, the Examples provided, and the cited

references are sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.

The art of catalytic antibody generation inherently involves some experimentation. The process requires the injection of a variety of different, but specific, haptens into an animal and then screening for the appropriate catalytic antibodies. This is the standard protocol in the art. Applying that protocol is not undue experimentation. The generation of catalytic antibodies, like the generation of conventional (non-catalytic) antibodies will not always be successful nor do those skilled in the art expect that each immunization will result in the creation of antibodies. Antibody generation involves an inherent uncertainty due to the hapten's immunogenicity, the selection of the transition state analog, the physiological state of the selected animal, etc. The detailed screening procedures provided in the specification assures the reliability of consistently obtaining the appropriate catalytic antibodies. The skill level in the art is high and the skilled artisan typically engages in such experimentation for the successful generation of antibodies. Such experimentation is reasonable and not undue. The following case law summarizes and explains the extent to which experimentation is permitted.

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue", not "experimentation." *In re Wands*, 858 F. 2d 731, 8 U.S.P.Q. 2d 1400, (Fed. Cir. 1988).
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988) and MPEP 2164.06.
>
> The test for enablement is whether one reasonably skilled in the art to make or use the invention from the disclosure in the patent coupled with information known in the art without undue

> experimentation. A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988).
>
> The enablement requirement is met if the patent application enables "any mode" of making and using the claimed invention. *William Service Group, Inc. v. O.B. Cannon & Son, Inc.*, 33 U.S.P.Q. 2d 1705, 1723 (Eastern District of Pennsylvania 1994). A patent application may be enabling even though some experimentation is required, but the amounts of experimentation must be reasonable. Id.
>
> An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni*, 561 F.2d 220, 224, 195 U.S.P.Q. 150, 153 (CCPA 1977), MPEP 2164.06.

Applicants, respectfully, direct the Examiner's attention to the following citations from Gao, the paragraph spanning pages 2216-2217 and the immediately following paragraph (which was also cited by the Examiner to show unpredictability, p.3 of the Official Action) which further demonstrate that the claimed invention is fully enabled. The following statements demonstrate a successful example of using a boron-containing hapten to elicit catalytic antibodies and the high reproducibility of the disclosed methodology:

> The observed rate enhancement supplied by BL25 reduced the half-life of the primary amide in **1a** from ca. 17.5 years to 3.9 h in the presence of the catalytic Fab and is >2 orders of magnitude higher than that observed for an antibody elicited by a phosphinate transition-state analog approach, highlighting the power of this direct selection strategy with the boronic hapten probe. (pp. 2216-2217)
>
> Finally, equally active protein was purified from three different fermentation batches. (p. 2217)

A copy of Nevinsky GA, Semenov DV, Buneva VN. *Catalytic antibodies (Abzymes) Induced by Stable Transition-State Analogs* Biochemistry (Moscow) 2000; 65(11): 1233-44 is enclosed for the Examiner's convenience as supporting reference material. Nevinsky et al.

provides twenty-four examples compiled in a comprehensive table format of successful catalytic antibodies productions where transition-state analogs were employed. This review further demonstrates that the claimed subject matter is fully enabled to one of ordinary skill in the art.

Applicants maintain that the extensive disclosure of the present specification, the disclosures in Gao and Nevinsky et al. and the high level of skill of workers in this art leads one to conclude that the claimed invention can be performed without undue experimentation.

Respectfully submitted,

KRAMER LEVIN NAFTALIS & FRANKEL LLP
Attorneys for Applicants

By: Barry Evans

Barry Evans
Reg. No. 22,802
(212) 715-7609